REMARKS/ARGUMENTS

Applicants appreciate the recent interview granted by the Examiner regarding this case. Applicants also acknowledge with appreciation the withdrawal of the previous rejection of claim 110 under 35 U.S.C. §112 (Office Action, page 2).

Please note that the Attorney Docket Number for this application has been changed from 20164000US5 to ARG010RC.

Claims 89, 91, 92, 94, 95, 99, 101, 103-113, 115-121 and 123-141 are pending in the application. Claims 123-139 have been cancelled. Applicants note that claim 114 was canceled in the previous Amendment (filed 26 September 2006). New claims 142-144 have been added to correct an oversight in the previous response in which claims 84-86, which had been rejoined to the pending claims, were inadvertently omitted from the claim listing; new claims 142, 143, and 144 are identical to previously pending claims 84, 85, and 86, respectively. Accordingly, no new matter has been added by way of amendment.

Independent claims 101 and 120 have been amended for clarification, as further discussed below. Accordingly, dependent claims 99, 103, 118, and 119 have been amended in order to maintain proper antecedent basis. Support for these amendments can be found in the application as filed, as further discussed in detail below.

No new matter has been added by way of amendment. Reexamination and reconsideration of the claims are respectfully requested.

The Invention

"The present invention provides for the first time a method of obtaining dendritic cells in sufficient quantities to be used to treat or immunize animals or humans with dendritic cells which have been activated with antigens" (specification at page 40, lines 25-28). Specifically, the invention provides "a method of producing cultures of proliferating dendritic cell precursors which mature *in vitro* to mature dendritic cells. The dendritic cells and the dendritic cell precursors produced according to the method of the invention may be produced in amounts suitable for various immunological interventions for the prevention and treatment of disease" (see the specification at page 19, lines 25-31 (the first paragraph of the Detailed Description of

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the Invention)). In this manner, the invention overcomes the previously existing problem in the art of not being able to obtain sufficient quantities of dendritic cells in culture for clinical treatment (as discussed, for example, in the Background section on page 2, second paragraph, and on page 8, lines 8-10). Further, dendritic cells produced by a method of the invention are "much more potent in presenting antigens to primed T cells than corresponding cultures of mature dendritic cells...." (see, *e.g.*, page 37, lines 17-20).

The Claims Meet the Requirements of 35 U.S.C. §112, First Paragraph

The Office Action has rejected claims 89, 91, 92, 94, 95, 99, 101, 103-121 and 123-141 under 35 U.S.C. § 112, first paragraph (Office Action of 13 December 2006, page 2, #5). Applicants note that claim 114 was canceled in the previously-filed Amendment of 26 September 2006 and that claims 123-139 have also been canceled. Applicants respectfully traverse this rejection with regard to the remaining claims.

The Office Action states that the rejected claims fail to meet the written description requirement because the specification and claims as originally filed do not provide support for the invention as now claimed. Applicants respectfully disagree with this conclusion.

Applicants note that claims 101 and 120 (and therefore also claims 89, 91, 92, 94, 95, 99, 103-113, 115-119, 121, 140-141, and new claims 142-144, which are dependent on or incorporate the limitations of claim 101) have been amended for clarification. Due to these amendments, dependent claims 99, 103, 118, and 119 have also been amended in order to maintain proper antecedent basis. Although Applicants believe that the previously pending claims met the written description requirement, it is hoped that these amendments to the claims will overcome the rejection and that the claims will be deemed allowable. In order to assist the Examiner, this paper includes the text of each passage cited for support either in a quote or in a footnote.

Support for the amended claims can be found throughout the specification, for example, on page 12, line 35 through page 13, line 2, which state that an "object of this invention is to provide novel immunogens comprising the dendritic cells or dendritic cell precursors of this invention which have been exposed to antigen and express modified antigen on their surface." Support for the other limitations of the claims has been discussed previously and includes, for

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example, discussion of the step of providing a tissue source (see, *e.g.*, page 19, line 32 through page 20, line 2[1]) and discussion of the importance to the claimed method of culture in GM-CSF (see, *e.g.*, page 24, lines 3-7[2]). The specification teaches that "GM-CSF has surprisingly been found to promote the proliferation *in vitro* of precursor dendritic cells. Cells are cultured in the presence of GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors" (see page 25, lines 19-24). Under these culture conditions, cell aggregates form which eventually give rise to dendritic cells (see, *e.g.*, page 28, lines 21-27[3] and page 27, lines 20-24[4]). Subculturing is discussed, for example, on page 28, lines 9-11[5] and 32-36[6]. Exposure of the cells to antigen and antigen fragmentation and presentation by the cells are discussed, for example, on page 36, lines 31-33[7] and on page 36, lines 14-16[8].

In addition, support for the amendment to claim 101 can be found in the priority application, USSN 07/861,612 filed 1 April 1992. Specifically, for example, original independent claim 17 and original dependent claim 36 of the priority application recite:

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[1] Page 19, line 32 through page 20, line 2 are as follows: "The starting material for the method of producing dendritic cell precursors and mature dendritic cells is a tissue source comprising dendritic cell precursors which precursor cells are capable of proliferating and maturing *in vitro* into dendritic cells when treated according to the method of the invention"

[2] Page 24, lines 3-7 are as follows: "Cells obtained from treatment of the tissue source are cultured to form a primary culture on an appropriate substrate in a culture medium supplemented with GM-CSF or a GM-CSF derivative protein or peptide having an amino acid sequence which sequence maintains biologic activity typical of GM-CSF."

[3] Page 28, lines 21-27 are as follows: "Cells are incubated for a sufficient time to allow the surface of the culture dish to become covered with a monolayer of tightly adherent cells including macrophages and fibroblasts affixed to which are aggregates of nonadherent cells. At this time, any nonadherent cells are removed from the wells, and the cellular aggregates are dislodged for subculturing."

[4] Page 27, lines 20-24 are as follows: "The primary cultures from the tissue source are allowed to incubate at about 37°C under standard tissue culture conditions of humidity and pH until a population of cells has adhered to the substrate sufficiently to allow for the separation of nonadherent cells."

[5] Page 28, lines 9-11 are as follows: "The nonadherent cells from the primary culture are subcultured by transferring them to new culture flasks at a density sufficient to allow for survival of the cells...."

[6] Page 28, lines 32-36 are as follows: "For serially subculturing the aggregated cells, the aggregated cells are dislodged from the adherent cells and the aggregated cells are subcultured on a total surface area of preferably between about 2 to 5 times that of the surface area of the parent culture."

[7] Page 36, lines 31-33 are as follows: "Cells should be exposed to antigen for sufficient time to allow antigens to be internalized and presented on the cell surface."

[8] Page 36, lines 14-16 are as follows: "Processing of antigen by dendritic cells or dendritic cell precursors includes the fragmentation of an antigen into antigen fragments which are then presented."

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17. A method of producing a population of mature dendritic cells from proliferating cell cultures comprising:

a) providing a tissue source comprising dendritic cell precursors;

b) treating the tissue source to obtain a population of cells suitable for culture *in vitro*;

c) culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain nonadherent cells and cell clusters;

d) subculturing the nonadherent cells and cell clusters to produce cell aggregates comprising proliferating dendritic cell precursors;

e) serially subculturing the cell aggregates one or more time to enrich the proportion of dendritic cell precursors; and

f) continuing to culture the dendritic cell precursors for a period of time sufficient to allow them to mature into mature dendritic cells.

36. A composition comprising antigen-activated dendritic cells wherein dendritic cells prepared according to claim 17 are pulsed with an antigen and wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells.

In view of the above amendments and discussion, and in consideration of the support throughout the specification as a whole and the specific support discussed above, Applicants respectfully request that the rejection of claims for lack of written description be withdrawn and the claims be deemed in condition for allowance.

The Rejection of Claims under 35 U.S.C. § 102(a) Should Be Withdrawn

The Office Action (page 6, #7) has maintained the rejection of claims 89, 91, 92, 94, 95, 99, 101, 103-121 and 123-141 under 35 U.S.C. § 102(a) over Pancholi *et al.* (1992) *Immunology* 76: 217-224. Applicants note that claims 123-139 have been canceled and that claim 114 was canceled in the previously-filed Amendment of 26 September 2006. Applicants respectfully traverse this rejection with regard to the remaining claims.

The Office Action states (page 6, #7) that the rejection over the Pancholi reference is maintained because although the Pancholi reference was published several months after the priority date of the present application, the "claimed cells are not supported by the instant specification [and] they are not supported by the priority documents, thus the priority date of the instant application is its filing date, 05/06/1998."

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In view of the claim amendments presented herein and the discussion above, Applicants respectfully submit that the claims as amended are fully supported by the specification and the priority documents and thus the priority date that should be accorded to the present claims is the official priority date of 1 April 1992. Accordingly, because the Pancholi reference was published in June 1992, several months after this date, it should not be citable against the present claims under 35 U.S.C. § 102(a). Therefore, Applicants respectfully submit that this rejection of claims should be withdrawn.

Nevertheless, Applicants note that, as discussed previously in this case (*e.g.*, in the Response filed 10 March 2006, page 11, third paragraph) and as required by the claims, the cells of the present invention are cultured in GM-CSF, which promotes the proliferation *in vitro* of precursor dendritic cells (see, *e.g.*, specification page 25, lines 19-23)[9]. "In the absence of GM-CSF, no colonies develop" (see page 26, line 19). Without forming colonies, the cells would be unable to form the enriched and expanded population of proliferating dendritic cell precursors required by the present claims. Pancholi merely teaches the isolation of dendritic cells directly from blood (see Abstract and also Materials and Methods section from page 218, left column, last paragraph through page 218, right column, first full paragraph). Thus, the process used to make Applicants' claimed cells is different from the process described by Pancholi, and the cells that result from the different process are also different. Thus, Pancholi does not teach the cells of the present invention.

There are at least two significant differences between the cells taught by Pancholi and the cells of the present invention. First, as discussed in the Background of the present specification, the present invention, by providing dendritic cells derived from an *in vitro* culture of a population of enriched and expanded proliferating precursor cells, overcomes the previously existing problem in the art of not being able to obtain sufficient quantities of dendritic cells in culture for clinical treatment (as discussed, for example, in the Background section on page 2, lines 18-25[10], and on page 8, lines 8-10[11]). Second, in contrast to the cells taught by Pancholi,

[9] Page 25, lines 19-23 are as follows: "GM-CSF has surprisingly been found to promoter the proliferation in vitro of precursor dendritic cells. Cells are cultured in the presence of GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors."
[10] Page 2, lines 18-25 are as follows: "[T]he use of [dendritic] cells is hampered by the fact that there are very few in any given organ. In human blood, for example, about 0.1% of the white cells are dendritic cells [citation omitted]

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dendritic cells prepared according to the methods claimed herein are more effective at presenting antigen to T cells *in vitro*. This aspect of the present invention is emphasized in the specification (*e.g.*, page 11, line 32 through page 12, line 1) and demonstrated by results obtained with dendritic cells prepared according to the claimed methods (see, *e.g.*, Figure 15A,which shows a significant proliferation of T cells in response to stimulation by immature or mature BCG-pulsed dendritic cells at DC:T cell ratios of 1:100 and 1:1000[12]). In contrast, Pancholi's dendritic cells show no stimulation of T cell response at a DC:T ratio of 1:100 (see Figure 2b). Thus, Pancholi's DCs show no stimulation of T cell response at a DC:T ratio of 1:100, while DCs prepared according to a method of the invention show a significant stimulation even at a much lower DC:T ratio of 1:1000. It will thus be readily appreciated that the cells of the present invention are more effective at presenting antigen to T cells *in vitro*.

Applicants note in this regard that the Examiner has previously acknowledged that the cells of the present invention differ from those described previously due to the requirement that the cells of the present invention are cultured in GM-CSF and the resulting effects of that culture requirement on the cells (see, *e.g.*, the Office Action of 13 August 2004, page 2, #2).

In view of the above discussion, Applicants respectfully request that the rejection of claims over the Pancholi reference for lack of novelty be withdrawn.

Claims 123-141 Meet the Requirements of 35 U.S.C. §112, First Paragraph

The Office Action (page 7, #9) has rejected claims 123-141 under 35 U.S.C. § 112, first paragraph, because "[t]he specification and the claims as originally filed do not provide support for the invention as now claimed." Applicants disagree with this conclusion, but in order to

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and these have not been induced to grow until this time. Similarly, previous studies [citations omitted] have not reported the development, in culture, of large numbers of dendritic cells from bone marrow."

[11] Page 8, lines 8-10 are as follows: "[N]either report [discussing the use of dendritic cells for therapeutic purposes] provides a method to obtain dendritic cells in sufficient quantities to be clinically useful."

[12] The methods disclose that 300,000 T cells were plated for these experiments (see description of experiments in Example 3, particularly on page 67, lines 29-31), and the number of DCs added for each data point is shown on the X-axis of Figure 15A. Thus, the data points in Figure 15A above the X-axis label "10^{3}" show results obtained with a DC:T ratio of 1,000 to 300,000, or 1:300, and the data points above the X-axis label "10^{2}" show results obtained with a DC:T ratio of 100 to 300,000, or 1:3000. These results show significant proliferation of T cells in response to stimulation by immature or mature BCG-pulsed DCs even at low DC:T ratios.

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advance prosecution, Applicants have canceled claims 123-141 without prejudice. Accordingly, this rejection has been obviated and should be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that all rejections have been overcome and that the claims are in condition for allowance. However, if the Examiner believes that any further discussion of this communication would be helpful, he is encouraged to contact the undersigned by telephone.

No additional fees or extensions of time are believed to be due in connection with this communication except for those indicated in documents accompanying this paper. However, if any additional extensions of time are necessary for the consideration of this paper, such extensions are petitioned under 37 CFR § 1.136(a). Please apply any charges that may be due for extensions of time or for net addition of claims to our Deposit Account No. 50-3187.

Respectfully submitted,

Leigh W. Thorne, Ph.D.
Attorney for Applicants
Registration No. 47,992

CERTIFICATE OF FACSIMILE UNDER 37 C.F.R. § 1.8 (a)

I hereby certify that this correspondence is being transmitted via facsimile (571-273-8300) to the United States Patent and Trademark Office on the date set forth below.

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